BRCA and Other Genetic Abnormalities

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Genes and Cancer

- All cancer is GENETIC
- Tumor suppressor gene:
  - a.k.a. “anti-oncogene”
  - Important in cell cycle control or DNA repair
- Proto-oncogene:
  - Normal gene that can become an oncogene due to mutations or increased expression
  - Helps regular cell growth and differentiation

What is Hereditary Cancer?

- Multiple close family members diagnosed with the same type of cancer
- Presence of related forms of cancer in the family (breast and ovarian, colon and endometrial, etc.)
- Individuals with multiple primaries (i.e. breast and ovarian)
- Early onset of diagnosis (< age 50 for breast or colon)
- Presence of rare tumors (male breast cancer, osteosarcoma, etc.)
- Ethnicity – some at higher risk of specific mutations

Etiology of Cancer

- 70-80% Sporadic
- 15-20% Family Clusters
- 5-10% Hereditary

General Features of Hereditary Cancer

- Attenuated/Familial Adenomatous Polyposis (Gardner syndrome, Turcot Syndrome)
- Birt-Hogg-Dubé syndrome
- Carney Complex
- Cowden syndrome
- Familial Malignant Melanoma
- Hereditary Breast and Ovarian Cancer
- Hereditary Diffuse Gastric Cancer
- Hereditary Leiomyomatosis and Renal Cell Cancer
- Li-Fraumeni syndrome
- Lynch syndrome (McCune-Albright syndrome)
- Multiple Endocrine Neoplasia Type I
- Multiple Endocrine Neoplasia Type II
- MYH-Associated Polyposis
- Neurofibromatosis type 1
- Nevoid Basal Cell Carcinoma syndrome
- Peutz-Jeghers syndrome
- Von Hippel-Lindau syndrome
- Xeroderma Pigmentosum

Hereditary Cancer Syndromes
Inheritance Patterns

- Most autosomal dominant
- Some autosomal recessive

Hereditary Cancer

- Who is appropriate for referral to genetics?
- What is included in risk assessment?
- Who should be tested?
  - And for what?
- How can genetic counseling/testing change care?

What does Risk Assessment Involve?

- Patient’s medical history
  - Cancer history, pathology, treatment
  - Carcinogen exposure
  - Reproductive health history
  - Hormone usage
  - Previous biopsies/surgeries
  - Other relevant physical features – colon polyps, dermatologic manifestations, etc.
- Family history
  - History of cancer, chemoprevention, prophylactic surgeries
  - Includes first-, second-, and third-degree relatives

Hereditary Breast Cancer
Hereditary Breast Cancer

- Half of hereditary breast cancer explained by mutations in BRCA1 and BRCA2
  - 1/500 individuals
- Other causes:
  - Cowden syndrome
  - Hereditary diffuse gastric cancer
  - Li-Fraumeni syndrome
  - Less well-characterized genes

Hereditary Breast and Ovarian Cancer

- BRCA1 and BRCA2
  - BRCA1 and BRCA2 predisposition genes 1 and 2
- Increased lifetime cancer risks
  - Breast: 50-85%
  - Ovarian: 15-45% (BRCA1 > BRCA2)
  - Pancreatic: 1-7% (BRCA2 > BRCA1)
  - Prostate: 20% (BRCA2 > BRCA1)
  - Melanoma: 2% (BRCA2)
  - Others? Perhaps uterine sarcoma, bile duct, stomach
- Increased risk for early-onset cancers
  - Risk of breast cancer before age 50: 30-50%

Ovarian: epithelial (usually serous adenocarcinoma)

Breast:
- Approximately 11-40% of women with triple negative breast cancer diagnosed ≤ age 40 have a BRCA mutation

Pathology

2013 NCCN Testing Guidelines

- More intensive screening protocol
  - Annual MRIs and mammograms, clinical breast exams
  - Ovarian cancer screening
  - Screening for men: prostate and male breast
- Medications
  - Birth control pills
  - Tamoxifen
- Prophylactic surgeries
  - Prophylactic mastectomies: 90% risk reduction
  - Prophylactic salpingo-oophorectomies: 96% risk reduction
- Prophylactic prostatectomy?

Medical Management

- http://brcatool.stanford.edu
4.5–9% of women undergoing risk-reducing salpingo-oophorectomies have occult ovarian cancers found pathologically.

One study showed 2/29 women undergoing risk-reducing mastectomies were found to have invasive breast cancer.

No surgery is 100% effective at eliminating risk.

- Primary peritoneal cancer

BRCA1, BRCA2, PALB2 work together to repair DNA double stranded breaks.

PARP1 is one step above and repairs single-stranded DNA breakage.

Inhibition of PARP leads to double stranded DNA breaks, which BRCA1/BRCA2/PALB2 would usually repair.

Too much damage overloads cell, leading to cell death.

Selective for cancer cells.

In clinical trials:

- Have been setbacks, but new trials beginning.

As part of the Affordable Care Act, BRCA testing now considered PREVENTIVE for unaffected women.

- USPSTF “B” recommendation

Insurance cannot apply co-pay, deductible, or co-insurance if a woman meets USPSTF criteria.

Only for women at high-risk (about 2% of adult women) and who have NOT had cancer.

However, ideally you first want to test someone who has had cancer.

- Non-Ashkenazi:
  - Any first-degree relative (or a second-degree relatives on the same side of the family) with breast or ovarian cancer

- Ashkenazi:
  - Any first-degree relative (or a second-degree relatives on the same side of the family) with breast or ovarian cancer

Myriad Genetics Laboratories lost patent to BRCA genes in June 2013.

"isolating genes found in nature is not patentable"

Now other labs can perform BRCA testing.

- Lower cost

- But are they as good?
Other Breast Cancer Syndromes

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Cancer Risks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cowden syndrome (PTEN)</td>
<td>25-50% breast, 10% thyroid, 5-10% endometrial, colon, renal, melanoma</td>
</tr>
<tr>
<td>Hereditary diffuse gastric cancer (CDH1)</td>
<td>30-57% lobular breast, 40-83% diffuse gastric, colon</td>
</tr>
<tr>
<td>Li-Fraumeni syndrome (TP53)</td>
<td>Overall risk in females &gt;90%, males 73%; breast, soft tissue sarcoma, osteosarcoma, brain tumors, leukemia, adrenocortical carcinoma</td>
</tr>
<tr>
<td>Peutz-Jeghers syndrome (STK11)</td>
<td>39% colorectal, 32-54% breast, 11-36% pancreatic, 30% gastric, 13% small bowel, 10% cervical, 10% uterine, 15% lung, 9% testicular, 21% ovarian sex cord tumors</td>
</tr>
</tbody>
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Breast Cancer Risk Assessment

- Even if no “hereditary” cause is present, a family history can lead to a higher risk of developing cancer
- Personal risk factors:
  - Nulliparity
  - Early menarche
  - Late menopause
  - Later age at having first child
  - Long-term hormone replacement therapy
- Statistical models available to estimate risk
  - Gail, BRCAPro, Tyrer-Cuzick (IBIS), Claus, BOADICEA

Breast Cancer Risk Assessment

- Gail model (National Cancer Institute)
- Tyrer-Cuzick Model (IBIS)
  - Also calculates likelihood of BRCA mutation (reliability?)

Breast Cancer Risk Assessment

- No model is perfect
  - All have strengths and limitations
  - All use certain factors to characterize risk
  - No single tool is comprehensive

Hereditary Colorectal Cancer
Majority of hereditary colorectal cancer caused by Lynch syndrome (2-3% of all colorectal cancer diagnoses)

- Five known genes: MLH1, MSH2, MSH6, PMS2, EPCAM
  - Gene-specific risks

<table>
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<tr>
<th>Cancer Type</th>
<th>General Population Risk</th>
<th>HNPCC Mutation Carrier Lifetime Risk</th>
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<tbody>
<tr>
<td>Colon</td>
<td>5%</td>
<td>100%</td>
</tr>
<tr>
<td>Endometrium</td>
<td>2.2%</td>
<td>20-44%</td>
</tr>
<tr>
<td>Stomach</td>
<td>&lt;1%</td>
<td>11-18%</td>
</tr>
<tr>
<td>Ovary</td>
<td>&lt;1%</td>
<td>5.1%</td>
</tr>
<tr>
<td>Renal/bladder</td>
<td>&lt;1%</td>
<td>5.3%</td>
</tr>
<tr>
<td>Small bowel</td>
<td>&lt;1%</td>
<td>4-9%</td>
</tr>
<tr>
<td>Brain/central nervous system</td>
<td>&lt;1%</td>
<td>1.9%</td>
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Colonscopy every 1-2 years, beginning at age 25
EGD with extended duodenoscopy every 3-5 years, beginning at age 30-35
Annual comprehensive physical exam beginning at age 25-30
Annual urinalysis beginning at age 25-30
Pancreatic cancer screening?

Women:
- Gynecologic cancer screening
  - Consider prophylactic hysterectomy + BSO after childbearing is complete

Always evolving and insurance-company dependent

- Amsterdam Criteria = 3-2-1 rule
  - 3 family members with Lynch-syndrome related cancers
  - 2 generations
  - 1 member diagnosed under the age of 50

Revised Bethesda guidelines
- CRC < 50
- Synchronous or metachronous Lynch-related tumors
- CRC < 60 with MSI-high histology
- CRC with ≥ 21° degree relative with Lynch-related tumor, at least one diagnosed ≤ age 50
- CRC diagnosed in ≥ 21° or 22° degree relatives, no age specified

Tumors (usually colorectal) can be screened for Lynch syndrome
- Immunohistochemistry for MLH1, MSH2, MSH6, PMS2
- Microsatellite instability

MSI-high pathology:
- Mucinous/signet ring cell
- Tumor infiltrating lymphocytes
- Crohn’s-like lymphocytic reaction
- Medullary growth pattern

1% of all colon cancers associated with Familial Adenomatous Polyposis (APC mutations)
- ~2-3/100,000 affected

FAP, attenuated FAP, Gardner syndrome, Turcot syndrome = same diagnosis (on a spectrum)
- FAP 100-1000s of polyps
- AFAP 10-100 polyps (average 30)

Important to differentiate between AFAP and MYH-associated polyposis
- Recurrence risk
- Medical management
Familial Adenomatous Polyposis

- **Cancer Risks – FAP:**
  - Colorectal: virtually 100%
  - Duodenal or peri-ampullary: 5-12%
  - Gastric: <1%
  - Thyroid (papillary): 1-2%
  - Hepatoblastoma (by age 5): 1-2%
  - Pancreatic: <1%
  - Medulloblastoma: <1%

- **Cancer Risks – AFAP:**
  - Upper GI, duodenal, and thyroid risks similar
  - Colorectal: 80%

Medical Management (FAP)

- Annual flexible sigmoidoscopy/colonoscopy beginning at age 10-15
- Total colectomy once polyp burden is too high
- Upper endoscopy: repeat based on findings, every 1-4 years
- Annual physical examination with abdominal palpation
- Regular small bowel screening (CT/MRI)
- Pancreatic cancer screening?

Other Cancer Syndromes

- **Syndrome**
  - **Von Hippel-Lindau syndrome (VHL)**
  - 5-17% pancreatic neuroendocrine, 70% clear cell renal cell carcinoma; hemangiolablastoma, pheochromocytoma, retinal angioma, endolympathic sac tumor
  - **Birt-Hogg-Dubé syndrome (PHCN)**
  - 13-34% renal cancer (chromophobe renal carcinoma); 8-14% pulmonary cysts, 80% folliculomas, renal oncaytomases
  - **Hereditary non-Von Hippel-Lindau Clear Cell Renal Cell Carcinoma**
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  - **Hereditary Leiomyomatosis Renal Cell Cancer (FLRC)**
  - Uterine fibroids at young age, 15% Type 2 papillary renal cell cancer

Other Colorectal Cancer Syndromes

- **Syndrome**
  - **MYH-associated Polyposis (MUTYH)**
  - 80% colorectal, 5% duodenal
  - **Juvenile Polyposis (SMAD4, BMPR1A)**
  - Juvenile-type polyps; 40-50% colorectal, 21% gastric, pancreatic, small bowel
  - **Hereditary Mixed Polyposis**
  - No specific estimate; individuals have multiple types of colon polyps
  - **Pena-Jeghers syndrome (STK11)**
  - See previous; risk of hamartomatous GI polyps
  - **Other Colorectal Cancer syndromes**
  - <1% of all colorectal cancers

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Many hereditary cancer syndromes have skin manifestations. Can be used to help guide testing or give a clinical diagnosis. Other tumors (not necessarily skin) may be significant:

- Osteomas (FAP)
- Lipomas (Cowden syndrome)
- Desmoid tumors (FAP)

### Skin Manifestations

- Trichilemmomas, papillomatous papules

### Cowden syndrome

- Sebaceous keratoacanthomas, epitheliomas, adenomas
- Muir-Torre variant

### Lynch syndrome

- Mucocutaneous freckling

### Multiple Endocrine Neoplasia Type II

- Mucosal neuromas (lips and mouth)

### Peutz-Jeghers syndrome

- Mucocutaneous freckling

### Hereditary Leiomyomatosis and Renal Cell Cancer

- Cutaneous (and uterine) leiomyomas
Familial Malignant Melanoma

- Multiple atypical or dysplastic moles

Birt-Hogg-Dubé syndrome

- Fibrofolliculomas, acrochordons, trichodiscomas

The Future is Now

- Former model of genetic testing: test for single most-likely syndrome, then follow up with other testing (if needed)
- New model of genetic testing: test initially for mutations in many different genes
  - Some genes not well understood or characterized
- Panels similar in cost (or sometimes CHEAPER) than single-gene testing
- What do we do???

Panels

- Comprehensive Cancer Panel (27 Genes)
- Breast Cancer Panel (25 Genes)
- Breast Cancer High-Risk Panel (10 Genes)
- Colorectal Cancer Panel (20 Genes)
- Lymphocytoxomal High Risk Panel (15 Genes)
- Pancreatic Cancer Panel (14 Genes)
- Renal Cancer Panel (27 Genes)

Other Genes

- ARL
- FAMF
- DMM1
- CDH1
- BRCA1
- FAMF2
- CDH1
- BRCA2
- FAMF3
- DMM2
- ATM
- BRCA1
- FAMF4
- CDH1
- BRCA2

Issues for Patients

- Meaning of results
- Telling other family members, including children
- Fear of developing cancer (perhaps again)
- Differing knowledge levels among healthcare providers
- Life, long-term care, disability insurance issues
- Health insurance coverage for increased screenings
- "Survivor guilt"
- Need unique support
How to Identify Patients at Risk

- Strong family history
- Younger than expected at diagnosis for that tumor type
- Unusual tumor type
- Unusual pathology
- Skin manifestations
- Use NCCN guidelines
- Call us!

Genomic Testing in Oncology

- Testing tumors to determine genetic profiles
  - Targeted therapy
- NOT a test for determining if someone has a hereditary cancer syndrome
- “Genetic” test on the tumor
  - Genetic mutations in tumor usually somatic
- Used for treatment decisions based on recurrence risk

Questions?

- Thank you very much!
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